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A STUDY OF SOME RECENT EXPERIMENTS ON SERPENT VENOM.

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The destruction of life from the bites of poisonous serpents is so extensive, the danger so insidious, and the fatal result follows so speedily, that at all times the subject has been one of especial interest and importance. The medical journals of India, as might be expected, abound with details of cases, of tests of supposed antidotes, and of experiments to determine the mode of action of the venom. Sir Joseph Fayrer states the average mortality from serpent-bites in India to be fully 20,000 annually. In 1869 the returns were obtained, through official sources, from a large part of India with unusual care and accuracy. In a population of nearly 121,000,000, representing an area of less than half the peninsula of Hindostan, the deaths were 11,416, or nearly one in 10,000.

Of these deaths, there were caused by—

Cobra	2,690
Krait (Bungarus ceruleus)	359
Other snakes	839
Unknown snakes	6,922
No details	606
	11,416

The number of deaths from "unknown snakes," which seems surprisingly large, is easily understood when it is remembered how general among the natives is the custom of sleeping on the ground. A person is bitten, and the snake escapes unseen in the darkness.

In 1880, 212,776 poisonous snakes were killed and paid for; and in 1881, 254,968.

Even in Europe, the number of accidents from snake-bite is very large. In one department of France, La Haute-Marne, the government paid, in six years, for the destruction of 17,415 vipers.

Before describing the recent researches of Lacerda, of Gautier, and of Weir Mitchell, which is more especially the object of this paper, it will be useful to make a brief summary of the most important investigations which had preceded them.

[1] Read before the Philosophical Society of Washington, May 19, 1883.

The first writer who published his experiments with serpent venom was Francisco Redi, an Italian. His observations on the viper appeared at Florence, in 1664.[1] His work was far surpassed in value by that of his countryman, Felix Fontana, whose "*Richerche filosofiche sopra il veneno della vipera*," was published at Lucca, in 1767. This classic work in toxicology has been translated into many languages. Fontana's experiments were 6000 in number, and are admirable for the patient care and fidelity with which they were conducted. His knowledge of physiological chemistry was, of course, limited, but many of his conclusions have been confirmed by modern researches.

In 1845, Prince Lucien Bonaparte analyzed the venom of the viper,[2] and discovered an active principle which he named *viperine* or *échidnine.* This was the first chemical analysis which had been made of serpent venom.

But the most important contribution to our knowledge of the subject is to be found in the elaborate series of experiments with rattlesnake venom, conducted by Dr. Weir Mitchell, of Philadelphia. His first account of them appeared in the *Smithsonian Contributions to Knowledge* for 1860, forming 117 quarto pages,[3] and his second essay appeared in the *New York Medical Journal* for January, 1868.[4] The earlier work begins with a full account of the anatomy of the head of crotalus, including the histology of the poison glands, and the action of the muscles concerned in the act of striking. This is followed by researches into the physical and chemical characteristics of the venom, and into the manner in which it acts upon cold-blooded and warm-blooded animals. Its effects on man, and the action of the principal known antidotes are next discussed, and an excellent bibliography completes the work. In his second essay, Dr. Mitchell announced some corrections of his views, as the result of further experiments. A brief account must be given of some of his more important conclusions.

Rattlesnake venom is a glutinous substance resembling a thick solution of gum acacia, in colour varying from a pale emerald-green to an orange or straw colour. Its specific gravity is about 1044. When completely desiccated it resembles dried albumen. Dr. Mitchell frequently tasted the venom and never perceived any pungency or acridity, or benumbing of the tongue, qualities which have been often attributed to it, as well as

[1] Osservazioni intorno alle vipera. Fr. Redi, Firenze, 1664.

[2] Ricerche chimiche sul velleno della vipera, pel Principe L. L. Bonaparte (letto in occasione della quinto unione degli Scienziati Italiani, tenuta in Lucca l'anno, 1843). Gazzetta toscana delle scienze medicofisiche. Firenze, 1843, p. 169.

[3] Researches upon the Venom of the Rattlesnake, with an Investigation of the Anatomy and Physiology of the organs concerned, by S. Weir Mitchell. Smithsonian Contributions to Knowledge, Washington, 1860, 4to. 117 pages.

[4] Experimental Contributions to the Toxicology of Rattlesnake Venom, by S. Weir Mitchell, New York Medical Journal, 1868. Also, Reprint.

to viper venom. Its reaction was always acid. It is unnecessary to give an account of the investigations made into its chemistry, as they are superseded by Dr. Mitchell's recent experiments. The toxicological effects of crotalus venom were the subject of a long series of experiments, which are fully detailed. The conclusions may be briefly stated.

Venom is harmless when swallowed. I. Because it is incapable of passing through mucous surfaces. II. Because it undergoes some change in the process of digestion which allows it to enter the blood as a harmless substance, or to escape from the intestinal canal in an equally innocent form. The rectum of the pigeon does not absorb the venom, and it produces no effect on the conjunctiva of animals.

The venom passes by endosmosis through serous membranes with great rapidity. Dr. Mitchell contrived to place a loop of the peritoneum of a chloroformed rabbit under the microscope; the circulation was beautifully exhibited, and, upon a drop of venom being deposited on the membrane, after the lapse of a minute, a sudden eruption of blood-corpuscles took place at the bifurcation of a capillary vessel followed by similar occurrences in other portions. The same phenomena appeared on the bared surface of muscles thus poisoned. This action, together with the defect of coagulability of the poisoned wound, accounts for the excessive hemorrhage about fang wounds.

In acute poisoning, where death rapidly ensues, the coagulability of the blood is not generally impaired, but where the symptoms are prolonged, the blood, after death, does not coagulate. The blood globules, according to Mitchell, are unaltered in venom poisoning, though he observed, in a few chronic cases, some disintegration of the edges. I shall recur to this point when speaking of Lacerda's and Halford's views. The cause of death, in acute poisoning in warm-blooded animals, is the cessation of respiration from paralysis of the nerve centres. The heart is enfeebled but not paralyzed. In chronic or secondary poisoning, the rapid decomposition of the blood and of the tissues locally acted upon, leave no doubt that serpent venom is a septic or putrefacient poison of astounding energy.

In his earlier experiments, Dr. Mitchell was led to believe that a rattlesnake's bite was fatal to itself, or to a fellow-crotalus. In his second essay, he comes very decidedly to the opposite conclusion. To this also reference will be made in connection with the poisonous snakes of India.

It is evident that, in experiments with venom, it will not do to depend upon the bite of the snake. If death do not follow, the escape may not be due to the virtue of an antidote but to the poison-gland having been recently emptied. Dr. Mitchell forced his snakes to bite the edge of a saucer into which the poison would drip. All his experiments were made by inoculating the venom thus obtained. From two to four drops are usually discharged at one bite, though fifteen drops were obtained from a snake which had been kept a long time in a box.

Dr. Mitchell's experiments as to antidotes resulted in the conviction of the absolute uselessness of the sulphites and hyposulphites, and the discovery that carbolic acid had no value as a true antidote, though it *delayed* a fatal result by interfering with the local circulation. This it does by its power to coagulate albumen. He mentions as a curious fact that some of the pigeons inoculated with venom and carbolic acid died with all the symptoms characteristic of poisoning by the latter powerful agent.

A case was, however, recently reported from Algeria[1] in which a French soldier was bitten by the Naja viper; alarming symptoms followed, but the application of a caustic, saturated, solution of carbolic acid, saved the man. Dr. Viaud-Grand-Marais also recommends this remedy.

It had been announced by Dr. Gilman,[2] in 1854, that serpent venom would destroy vegetable life. Dr. J. H. Salisbury made a similar declaration.[3] Their experiments were few, ill-guarded, and inconclusive, but Dr. Mitchell pursued the inquiry with all necessary precautions, and found no ground whatever for such a belief. I may add that a French surgeon, who has published his researches into the poison of the viper, M. Viaud-Grand-Marais, positively denies that it has any effect on plants.

The late Mr. Darwin made some experiments with cobra poison on *Drosera*. He says: "I felt sure that the leaves were killed; but after eight hours' immersion they were placed in water, and, after about forty-eight hours, they re-expanded, showing that they were by no means killed. The most surprising circumstance is that, after an immersion of forty-eight hours, the protoplasm in the cells was in unusually active movement. . . . Hence I cannot doubt that this poison is a stimulant to the protoplasm."[5]

The next important work, following Dr. Mitchell's essays, is that of Dr. Joseph Fayrer, of Calcutta, now Sir Joseph Fayrer, President of the Medical Board of the India Office. It is entitled: "The Thanatophidia of India, being a description of the Venomous Snakes of the Indian Peninsula, with an account of the Influence of their Poison on Life, and a Series of Experiments. London, 1872. Imp. folio, with thirty-one plates." This is a superb work, revelling in all the luxury of finest paper, blackest print, and beautifully coloured plates. The experiments were continued through three years, and, though chiefly made upon cobra venom, include the effects of some other poisonous serpents. There are twenty-one fami-

[1] De la morsure de la vipère Naja en Algérie, et de son traitement par l'acide phénique. Par M. Jacquemet. Rec. de mém. de méd. mil. etc. Paris, 1881, 3e sér. 226.

[2] On the Venom of Serpents. B. J. Gilman, St. Louis Med. and Surg. Journal, 1854, p. 25.

[3] Influence of the Poison of the Northern Rattlesnake (Crotalus durissus) on Plants. J. W. Salisbury, N. York Journ. Med. 1854, U. S., XIII. p. 337.

[4] Dict. encyclop. des sciences médicales, 1881, *sub voce* Serpents venimeux.

[5] On the Nature and Physiological Action of the Crotalus-poison as compared with that of *Naja tripudians* and other Indian Venomous Snakes, etc. By T. Lauder Brunton and J. Fayrer. Proc. Roy. Society, 1875, No. 179. Also, Reprint.

lies of Indian snakes, of which seventeen are innocuous. The four poisonous families are divided into two groups. I. Colubrine, which includes the Elapidæ and Hydrophidæ. II. Viperine, including the Viperidæ and Crotalidæ. The experiments were made upon the ox, horse, goat, pig, dog, cat, civet, mongoose, rabbit, rat, fowls, kites, herons, fish, harmless snakes, poisonous snakes, lizards, frogs, toads, and snails. As regards these creatures, he arrived at the following conclusions: Snake poison acts with most vigour on the warm-blooded animals; birds succumb very rapidly; a vigorous snake can destroy a fowl in a few seconds. The power of resistance is generally in relation to the size of the animal, though not altogether so; cats, for example, resist the influence of the poison almost as long as dogs three or four times their size. Cold-blooded animals also succumb to the poison, but less rapidly. Fish, non-venomous snakes, mollusca, all die. After death from cobra poison, the blood coagulates, but generally remains fluid after viperine bites.

Fayrer's experiments confirm those of Weir Mitchell, that poisonous snakes are not injured by their own venom or that of other poisonous snakes. He found, however, that the smaller and less poisonous varieties were affected by the bite of the cobra or daboia, though very slowly. From his description of the symptoms in these cases, it may be inferred that the local injury was followed by blood-poisoning, probably due to the development of micrococci.

In one important respect, Fayrer's conclusions differ from Mitchell's. He asserts very positively that snake-poison is deadly when applied to a mucous membrane, to the stomach or conjunctiva. He goes on to state that the blood of an animal, dead from snake-poison, is itself poisonous; if injected into another animal, death ensues, nevertheless the fowls and pigeons killed in his experiments were greedily sought for by his attendants, who ate them with impunity. As the process of cooking cannot destroy the deadly qualities of venom this fact strongly militates against Fayrer's theory. He found that venomous snakes, though not at all affected, or very slightly, by snake-poison, are yet very susceptible to other poisons, such as strychnia or carbolic acid. The latter destroys them very rapidly, and they seem to have a great aversion to it.

Sir Joseph Fayrer tested every known or asserted antidote, but the results were, in every case, unfavourable. The ligature, excision, and general treatment seemed to give the only chance for life, and they were often powerless. It seems reasonable, however, that experiments upon such small and susceptible animals as fowls and pigeons should not be held as conclusive against the possible virtue of an antidote, in poisoning of large mammals, including man.

Having thus rapidly sketched preceding investigations and discoveries, we come to those of recent date.

Dr. J. B. de Lacerda, Director of the Physiological Laboratory of the National Museum of Rio Janeiro, has been, during the last ten years, ex-

perimenting with the venom of Brazilian snakes, especially with that of Bothrops jararacassu, a serpent which closely resembles its congener, the North American crotalus, in the intensity of action of its venom. During that time, he has made several communications to the French Academy of Science.

In 1872, Lacerda announced that he had discovered "figured ferments" in the venom of serpents.[1] He placed a drop of rattlesnake venom under the microscope and saw the production of spores take place. The spores increased by scission and by internal nuclei. This has not been confirmed by further experiments.

The blood of a poisoned animal presented the following phenomena: the red corpuscles began by presenting little shining points which increased until the globule broke down, and was replaced by numerous ovoid corpuscles, very brilliant, and possessed of oscillatory movements. The blood obtained from animals which had died from the serpent's venom, when injected into others, hypodermically, invariably produced death in a few hours. It will be remembered that Mitchell did not observe any change in the red blood corpuscles to any marked extent.

Further experiments were made in 1879[2] and 1880[3] by Lacerda, assisted by Dr. Couty, a pupil of Claude Bernard. This time they employed the venom of the *Bothrops jararaca*, which is held to be less potent than that of the *jararacassu*, in order to test the effect of local injections. These were made in all the tissues of the body, in the muscles, the heart, the pleura, the brain, the intestines, the stomach, and, by means of a laryngo-tracheal sound, in the substance of the lungs.

Wherever injected, unless there was vascular rupture, or an antecedent wound, there were no signs of the poison having entered into the blood. On the contrary, local evidences of inflammation were invariably produced, often of great intensity, such as phlegmonous abscess, meningo-encephalitis, acute pleurisy or pneumonia.

Of all the tissues, the lungs seemed to be the most sensitive to the effects of the venom, and death ensued almost as rapidly as when the injection was made into the blood. The intestines were very slow to absorb the poison, the stomach, above all, being almost insensible to its effects.

In 1881, a continuation of these experiments was practised on monkeys and frogs. The effect on monkeys, whether the poison were injected into the veins or into the tissues, was more rapid than on the dogs which had been the subjects of the previous experiments; while, as was to be expected, the effect upon frogs was proportionately slower. The fatal dose for a monkey, compared to that requisite for a frog, regard being had to their proportionate weight, was about 1 to 1000.

[1] Comptes rendus, Acad. d. sc., Paris, 1877, lxxxvii. 1093–1095.

[2] Ibid., 1879, 372–6.

[3] Ibid., 1880, 549.

But the most interesting of Lacerda's discoveries was reported to the French Academy of Sciences in September, 1881. After proving the inefficiency of various supposed antidotes, such as perchloride of iron, borax, tannin, and other substances, he found that the permanganate of potassium produced very remarkable results. He obtained his supply of poison by forcing the bothrops (the more deadly variety), to bite cotton-wool, and the venom which poured out upon it was dissolved in eight to ten grammes of distilled water. A syringeful of this solution was injected into the cellular tissue of the thigh or groin of a dog. In from one to two minutes after, the same quantity of a filtered one per cent. solution of permanganate of potassium was injected. The dogs, examined the next day, exhibited no evidence of injury, except a trifling local irritation at the point of injection. Nevertheless, this same solution of venom, injected into the tissues without the counter-poison, produced great swelling, abscesses, and extensive loss of substance.

Lacerda next injected the poison into a vein, and here again, the permanganate was found to be of signal efficacy. Out of 30 experiments, two only were unsuccessful, the failures being attributed to the bad condition of the dog in one case, and to the too great delay in administering the remedy in the other. A solution was made in 10 grammes of water of the venom obtained from 12 to 15 bites of a bothrops. Half a syringeful of this was injected into a vein and 2 c. c. of a one per cent. solution of the permanganate was injected, half a minute later. Beyond a slight agitation and quickening of the pulse, the dogs betrayed no disturbance or uneasiness. They were watched for several days.

In another series of tests, the experimenters waited until the characteristic symptoms of poisoning began to exhibit themselves, and when the pupil was largely dilated, the respiration embarrassed, the heart beating rapidly, and the feces and urine were involuntarily discharged, the solution was rapidly injected. At the end of two or three, and sometimes five minutes, the various symptoms would disappear, although a general prostration would remain for some time. As this lessened the dog would begin to walk and would finally recover. In all cases the solution was tested by injection into the veins without the antidote, and, in every instance, the dog died.

Lacerda formally expresses his belief that the permanganate of potassium is a positive antidote for serpent poison. His experiments were, many of them, performed in presence of the Emperor Pedro, and other persons of distinction in science.

Dr. Badaloni, of Bologna,[1] repeated the experiments of Lacerda and Couty, but without the same success. This was, I think, largely due to his different method of proceeding. Lacerda inoculated the venom, pre-

[1] Sul valore del permanganato di potassa quale antidoto del veneno dei serpenti (ofidi). Rapporto del Giusseppe Badaloni. Bologna, 1882. 8vo.

viously obtained, so that there could be no doubt as to the poisoning taking place. Badaloni compelled the viper, the serpent he employed, to strike the animal experimented on. Of course, there could be no certainty that venom was injected, except from the symptoms. Further, Lacerda injected the antidote through the same punctures by which the venom had penetrated, while Badaloni injected it into the neighbouring tissues. In his first experiment, a rabbit was bitten on the upper lip and on a paw, and the permanganate solution was injected into the tissues of the shoulder; in fifteen minutes the rabbit died. In a second case, when the antidote was injected, two minutes after the evidences of poisoning manifested themselves, the rabbit recovered; but so did a third rabbit, without any treatment. The fourth rabbit was bitten by two vipers, and the permanganate was injected fifty-five minutes after the first bite and thirty minutes after the second; this rabbit recovered.

Badaloni's experiments are inconclusive, but are interesting from the fact that he records the temperature of the poisoned animal every three or four minutes. The temperature before the bite was almost uniform at 39.5° centigrade, and it fell in one case to 34.5°, with a steady rise as the danger diminished.

Mr. Vincent Richards,[1] of Calcutta, who had been a member of the Snake-poison Commission, upon hearing of Lacerda's investigations, instituted a series of experiments upon the effect of the permanganate on cobra poison. His conclusions were, that the salt, though not an antidote, strictly speaking, was of very considerable value in the treatment of snake-bites; that it had the power to neutralize the venom in the tissues, but had no effect if the poison had been absorbed into the general circulation. Sloughing, he found to be an almost constant result of the injection of the permanganate. His experiments as to the strength of the solution required, resulted as follows: He mixed $3\frac{1}{2}$ centigrammes (about $\frac{1}{2}$ grain) of cobra-venom with the solution and injected it into the cellular tissue of a fowl.

With a	$\frac{1}{8}$	of	1-per-cent.	solution,	the fowl	died in	13	minutes.
"	$\frac{1}{4}$	"	"	"	"	"	11	"
"	$\frac{1}{2}$	"	"	"	"	"	18	"
"	$1\frac{1}{2}$		"	"	"	"	59	"
"	2		"	"	the fowl became somewhat sluggish, but recovered.			
"	4		"	"	the fowl was not affected at all.			

Permanganate of potash is, according to Le Bon, the most powerful disinfectant known, but he states that it exerts but little influence upon microbes.[2] This is a view generally held by those who have experimented with antiseptics; but Dr. G. M. Sternberg, in an article upon

[1] Indian Med. Gazette. Calcutta, 1882, xvii. 1; 57; 85.

[2] Comptes rendus, 1882, ii. 259.

germicides in this Journal for April, places it second in rank as destructive of germs.

Mr. Richards advises the use of a 5-per-cent. solution, and that, after the injection, the parts should be kneaded and pressed with the fingers, so as to distribute the antidote.

Lacerda's method was also tried by Theodor Aron, an assistant of Professor Binz, of the University of Bonn.[1] His experiments were made with cobra-venom which had been sent from India, in a dried state. He mentions that a part of the solution which had become absolutely putrid was scarcely at all diminished in its virulence. Of 13 rabbits inoculated with the poison, and treated with the permanganate of potassium, 7 died. He had greater success with a solution of chloride of calcium, for in 22 experiments with that antidote he saved 17 of the rabbits. He tried the effect of alcohol, of caffeine, atropine, and brucine, but all proved valueless. Aron's experiments appear to have been carefully made. He inoculated two rabbits with the same quantity of venom in each instance, and administered the antidote to one only. The other always died.

In the *Journal d'Hygiène* for September 22, 1881, Dr. de Fourier mentions having received a letter from a captain of engineers, dated at Banana de Itaguaby, in Brazil. Captain Rezende says:—

> "While we were measuring the grounds around the imperial farm of San Luiz, one of our surveyors was bitten above the heel, about two o'clock in the afternoon, by an enormous serpent, the *jararaca pregnicosa*,[2] which measured a metre and a half in length. Before leaving Rio I had provided myself with a bottle of the solution of permanganate of potassa, recommended by M. de Lacerda, and immediately made five hypodermic injections with it, two into the wound itself and three above the instep. The patient also drank a teaspoonful of the solution. At the time I write, eight o'clock in the evening, the surveyor limps a little, but has none of those terrible symptoms which always follow the bite of this serpent."

Professor Vulpian, in a note read to the Academy of Sciences in Paris, a short time since,[3] commenting on Lacerda's experiments, declared the permanganate of potassium to be dangerous to life when introduced into the circulation. Half a gramme of the salt which he injected into the jugular vein of a small dog produced death. A great many experiments have been made, especially by Sir Joseph Fayrer, to test the action of supposed antidotes when injected into the veins or tissues of animals, without the accompaniment of the venom, and conclusions have been drawn as to their poisonous qualities, as in this statement of Vulpian's. It may be doubted whether these conclusions are warranted. The presence of venom

[1] Experimentelle Studien über Schlangengift. Von Theodor Aron. Centralblatt f. klin. Med., 1882, No. 31, Nov. 18.

[2] I suppose this is a printer's blunder for *perniciosa*; or it may be meant for the Portuguese word *preguiçosa*, sluggish.

[3] Comptes rendus, 1882, xciv. 614. Études expérimentales relatives à l'action que peut exercer le permanganate de potasse sur les venins, les virus et les maladies.

in the blood or tissues may modify the otherwise toxic action of the antidote. It certainly does in the case of stimulants; alcohol is tolerated, without ill effects, in quantity sufficient, at other times, to produce excessive intoxication, if not even coma.

Before leaving the subject of Lacerda's experiments, a curious circumstance remains to be told. Dr. Couty, his assistant, sent a communication to the Academy of Sciences, which was read at the meeting of April 24, 1882, in which he reverses the opinion he had previously expressed, and declares that the permanganate does not even mitigate the activity of the bothrops venom when the latter is injected into the veins. He admits, almost unwillingly, that it decomposes the venom in the tissues. Dr. Couty gives an account of a few experiments he had made, in all of which the dogs operated upon died.

Lacerda has not, as yet, made any communication to the Paris Academy in reply to this statement of his former coadjutor, but he addressed a note to the Jornal do Commercio, published at Rio de Janeiro, in which he alludes delicately to the fact that the friendly relations between himself and Dr. Couty had been interrupted, and that, consequent upon that condition, came this surprising recantation of the latter.[1] He points out that in Couty's latest experiments, 2 c. c. of a saturated solution of venom, representing fifteen or sixteen bites of the bothrops, were injected directly into the circulation, and that the remedy could not overtake it when in such deadly quantity. Further, he asserts that the permanganate is a chemical antidote, and not a physiological one, that contact, and speedy contact, is therefore necessary. He reasserts the conclusions drawn from his numerous experiments. He might have added that injecting the venom into one saphena vein, and the antidote into the other, unnecessarily increased the danger of absorption, and that a one per cent. solution of the salt was too feeble as against the concentrated venom employed. In short, the experiments seem rather to have been planned to produce a failure, and their negative results cannot be set against the positive success of Lacerda, and that of Richards and many others, with the more deadly cobra poison.

The records of scientific research afford many surprising instances of contemporaneous discovery—discoveries with identical results, made at nearly the same time by independent observers. About the time that Lacerda was experimenting with the venom of the bothrops in Brazil, Dr. Armand Gautier, of Paris, arrived at very similar conclusions as to the neutralizing power of caustic potassa in relation to cobra or rattlesnake venom. His communication upon the subject was read at a meeting of the Academy of Medicine, July 26, 1881.[2] Lacerda's paper was presented to the Academy of Sciences September 2, but as it was sent from Brazil,

[1] O permanganato de potassa contra a mordedura de cobras. Gaz. med. de Bahia, 1882, 2 s. VI., 550–559.

[2] Bull. Acad. de méd. Par., 1881, 2e sér., X., 779; 948.

it is clear that the two investigators arrived at similar conclusions about the same time.

Gautier's experiments with serpent venom arose during his researches into the nature of the ptomaines. A word or two of explanation as to the nature of these substances may be necessary. Ten years ago, Selmi, of Bologna, discovered in a cadaver certain alkaloids closely resembling the well-known vegetable alkaloids, such as aconitine, veratrine, morphine, and others. These new bodies were the products of putrefaction, and he called them ptomaines, from πτῶμα, a carcass. Strange to say, nearly about the same time, Gautier also discovered these alkaloids to be developed in putrefied blood. Further investigations have shown that ptomaines are also found in the living body, and they have been discovered in the urine of fever patients, in healthy urine, saliva, blood, muscular juice, in the serum of ovarian cysts, in the amniotic fluid, and in some other animal fluids.

When it is remembered that these ptomaines are violent poisons, that they respond to reagents just as the poisonous vegetable alkaloids do, differing only in the *velocity* with which the reducing power is exerted, that they are produced in certain morbid states of the living body, and are generated by putrefaction in the cadaver, we must admit the enormous importance of the discovery in its relation to medical jurisprudence. Brouardel speaks of it as the "sword of Damocles" hanging over the head of the expert in toxicology.

Time will not admit of more than this mere mention of the subject, but its relation to serpent-venom remains to be told. Gautier obtained from healthy saliva sufficient ptomaine to destroy birds. The saliva was procured direct from the duct of the parotid gland, so that it was uncontaminated by the impurities of the mouth. The points of resemblance of serpent-venom to the new alkaloids are as follows: they are not ferments; heat long applied leaves them both nearly as deadly as before. Gautier boiled the serpent-venom, filtered it, and evaporated it to dryness; still, when dissolved in water or glycerine, it would destroy life. He exposed it to a temperature of 125° C. for several hours, without diminishing its potency. The toxic effect upon animals is the same with both. At first is observed restlessness, then rapid breathing, coma, paralysis, convulsions, and death with the heart in systole. After death, the muscles do not contract under the stimulus of the electric current. Professor Corona[1] says the loss of muscular contractibility is produced by none of the vegetable alkaloids excepting muscarine, the active principle of poisonous fungi, which strongly resembles the ptomaines in its effects. Both serpent venom and ptomaines respond alike to chemical tests, and have the same reducing power. A singular peculiarity has been observed in both of

[1] Gianetti e Corona. Sugli alcaloidi cadaverici o ptomaïne del Selmi. Memoria letta all' Accad. di Sassari, XIX. Adunanza, 1880.

them, that the gastric juice increases their virulence, while the admixture of bile diminishes it.

In the course of his experiments, Gautier found that the injection of a solution of caustic potassa into the veins or tissue, in combination with cobra venom, made the poison innocuous. When it is remembered that the permanganate of potassium is soon decomposed in the blood, and caustic potassa remains, the identity of the discovery and conclusions with those of Lacerda is evident and remarkable.

Dr. Corre, of the French Navy, some time since gave an account of the symptoms produced by certain poisonous fishes in tropical countries, and they strongly resemble the effects just described, of ptomaines and serpent poison. M. Remy finds that the genital organs, the ovaries, and the testicles, are the poisonous parts. A bouilli made from them and injected under the skin of two dogs produced death, while the other parts of the fish proved to be inert.[1]

Before leaving the subject of the ptomaines, I wish to draw attention to a passage in Dr. Weir Mitchell's account of his experiments with rattle-snake venom, published in 1868.[2] He said: "The one form of poison which most resembles venom is that of putrefactive substances, and I am inclined to think that from putrefying material may yet be separated a substance, which, concentrated, will prove active toxically, and will, perhaps, enable the observer to repeat the facts I have witnessed here." This prediction was made in 1868, three years before Selmi made known his discovery of the cadaveric alkaloids.

The ptomaine theory would be incomplete without reference to another pathological process in which the omnipresent bacteria figure. It is believed by Gautier, Le Bon, Dr. Ogston, of Edinburgh, and others, that these micro-organisms, when in large quantities, engender ptomaines.

They argue that when a small inoculation is made into the tissues—for it must be understood that this form of the germ-theory involves tissue-poisoning rather than blood-poisoning—the blood acting only as the carrier—a rapid increase of micrococci takes place, with local irritation and subsequent pyæmia. If a larger quantity of the poisonous fluid be injected, ptomaines are developed in proportionate amount, and a fatal result rapidly follows.

It cannot be said that the development of ptomaines from micrococci, or of the latter from the former, for both views have been maintained, is anything more than a hypothesis—proofs are, as yet, wanting. But, all theory apart, there is no doubt as to the fact that, while inoculation of serpent-venom or animal-poison into the blood or tissues, in large quantity, or of a specially virulent quality, will produce rapid death by paralysis of the

[1] Note sur les poisons toxiques du Japon. Comptes rendus Soc. de biologie, 1883, iv. 263.

[2] Experimental Contributions, etc., p. 23.

nerve-centres, smaller injections, or of a less virulent material, will produce great local irritation and even gangrene, followed by septicæmia and probably death.

There appears to be some similarity to the latter process in the action of the *sui*, or needle-poison, of India.[1] The seeds of the Abrus precatorius, known as *rati* or *gunchi* seeds, are used as an article of food in times of scarcity, but if the powdered seed, even in small quantity, be injected into the cellular tissue, it produces inevitably fatal effects. The *chamars*, or skinners, as they are called, robbers who steal or destroy cattle in order to sell the hides, make the powder into a paste, and form from it the *sui*, or needle, which is a spike about three-quarters of an inch in length, resembling a cock's spur. It becomes very hard and sharp when dry, and, having been inserted into a wooden handle, it is driven by a forcible blow into the skin of the animal. Some instances have recently occurred of its fatal use on human beings, and the composition of the *sui* poison has been made the subject of official investigation. At one time it was supposed to be dried serpent venom, but its effects are different. There is neither paralysis, difficult respiration, convulsions, or coma, as in acute serpent-poisoning. As the *sui* liquifies, it produces intense cellulitis, with inflammation of the lymphatics, and, as it slowly finds its way into the circulation, great depression of the vital powers ensues, ending in death. Extreme weakness with local swellings are the only symptoms. Two dogs, which were experimented upon with it, died, the one in 49, and the other in 55 hours. It is very probable that when a competent observer investigates these cases, he will find the tissues and fluids of the poisoned animal swarming with bacteria.

It is not within the scope of this paper to relate the results obtained with the various remedies for serpent poison, except in connection with recent experiments, but a few words must be said as to the value of ammonia injected into the veins or tissues. The evidence in regard to this remedy is contradictory and puzzling.

Professor George B. Halford,[2] of the University of Melbourne, has recorded many cases, observed by himself and others, in which the use of ammonia seemed wonderfully successful. His experiments upon animals were made with the venom of the tiger-snake (*Hoplocephalus curtus*). It has been objected that the bite of Australian serpents is not generally dangerous. Sir Joseph Fayrer, and other Indian observers, have found ammonia entirely worthless as an antidote to cobra-poison. Dr. Weir Mitchell states that it has no value as a chemical antidote, and as a stimulant it is far inferior to alcohol. Professor Halford asserts that serpent venom produces an enormous increase of the white corpuscles of the blood, and he attributes this to a germinal matter consisting of nuclei $\frac{1}{4000}$ inch

[1] Indian Med. Gaz., Calcutta, 1882, xvii. 287.

[2] The Treatment of Snake-bites in Victoria, Melbourne, 1870, 8vo.

in diameter, proceeding from the serpent's glands. Dr. Weir Mitchell's views are quite adverse to this belief. Prof. Halford further insists that death from snake-bite is due to deoxidation of the blood, the addition of the germinal matter from the venom, in some unknown manner, destroying its power of absorption of oxygen. He asserts that the blood of poisoned animals will, after death, speedily absorb oxygen to a much larger extent than unpoisoned blood.

A case has recently been reported in which the new remedy, jaborandi, was employed with success in a case of snake-bite.[1] Profuse salivation and perspiration was produced, followed by the subsidence of the dangerous symptoms.

Dr. Weir Mitchell has again entered the field of experiment, but this time his investigations have been made with the assistance of Dr. Edward Reichert,[2] upon the venom of the Gila monster, the *Heloderma suspectum*. This is the only member of the lizard family which is, as yet, known to be poisonous. Last November a specimen which was in the Smithsonian Institution, while being examined by Dr. Shufeldt, bit him in the thumb, inflicting a severe, lacerated wound. The doctor sucked the wound until bleeding ceased, but the hand began to swell, and such severe pain shot up the arm and down the corresponding side, that he fell fainting to the ground. A sleepless night followed, but in a few days the wound healed entirely. The same lizard was sent to Dr. Mitchell, who obta ned its saliva by forcing it to bite a saucer, into which the secretion dribbled. The saliva had a faint, aromatic odour, and was distinctly alkaline, in contrast to serpent-venoms, which are all acid.

About four minims of this saliva, diluted with half a c. c. of water, was thrown into the breast muscles of a large, strong pigeon. In three minutes he began to rock on his feet, respiration became rapid, short, and then feeble, convulsions with dilated pupils followed, and before the end of the seventh minute, the bird was dead. In another experiment, in which one-sixth of a grain was injected into the carotid artery of a rabbit, the animal died in nineteen minutes; and, in another case, death ensued in a minute and thirty-five seconds. After many other tests of its virulence, Dr. Mitchell comes to the following conclusions: The poison of Heloderma causes no local injury; it arrests the heart in diastole, the organ contracting slowly after; the heart loses its irritability to electric stimuli at the time it ceases to beat; the other muscles and nerves respond readily to irritants; the spinal cord has its power annihilated abruptly, and refuses to respond to the most powerful electric currents.

[1] Morsure de vipère; accidents graves; emploi du jaborandi; guérison. Gaz. hebd. de méd. et de chir., Paris, 1882, 2e sér., xix. 835.

[2] A partial study of the poison of Heloderm suspectum (Cope), the Gila monster. By S. Weir Mitchell and Edward T. Reichert. Medical News, Phila. 1883, xiii. 209–212. Also, Reprint.

This interesting and virulent heart-poison contrasts strongly with the venoms of serpents, since they give rise to local hemorrhage, and cause death chiefly through failure of the respiration, and not by the heart, unless given in overwhelming doses. They lower muscle and nerve reaction, especially those of the respiratory apparatus, but do not, as a rule, cause extreme and abrupt loss of spinal power.

Dr. Mitchell has made arrangements to have a number of these lizards sent to him in the spring, when he will prosecute his investigations into the nature of their venom. The Gila monster grows to the length of three feet; the specimen which bit Dr. Shufeldt was fourteen inches long.[1]

In the *Virginia Medical Monthly* for February, is an article by Dr. Isaac Ott, of Easton, Pennsylvania, entitled: "The Physiological Action of the Venom of the Copperhead Snake—Trigonocephalus contortrix." In Dr. Ott's experiments, the snakes were forced to strike the rabbit or frog, a method, as before stated, lacking in precision. One rabbit died in two hours; another, which had been struck by three copperheads, in eight minutes.

Dr. Ott's principal conclusions are as follows:—

The venom of the copperhead is weaker than that of the rattlesnake.

Both reduce the heart's action, and, in cases of large quantities of venom, death ensues through the heart.

Muscular irritability at time of death is little affected in copperhead poisoning.

The cardiac force, rhythm, and frequency, and the arterial tension are lowered by both venoms.

The blood after copperhead poisoning shows no microscopic changes of its globules, or any difference in its spectrum.

Dr. Ott, like Dr. Mitchell in his experiments with heloderma, made use of the kymographion, and recorded the variations of pulse and arterial tension. Neither of them seems to have made any record of the temperature.

The latest, and from the standpoint of physiological chemistry, the most important addition to our knowledge of the subject is again the work of Dr. Weir Mitchell. At the recent meeting of the National Academy of Science, in this city, Dr. Mitchell read a paper describing the results of some researches made by himself and Dr. Edward T. Reichert,[2] with the fresh venom of the rattlesnake, copperhead, and moccasin. The report says: "Our work has resulted in the isolation of three distinct proteid bodies, of which two are soluble in distilled water and one is not. Of the

1 The bite of the Gila monster (Heloderma suspectum, Cope). *Am. Naturalist*, Philada., xvi. 907–9.

2 Preliminary Report on the Venoms of Serpents. By S. Weir Mitchell and Edward T. Reichert. (Read before the National Academy of Science, April 18, 1883.) *Med. News*, Philada., 1883, xlii. 469–472. Also, Reprint.

former two, one is incoagulable at a temperature of 100° C. It may be obtained by boiling venom, which throws down or destroys all the other proteids, and then filtering, or by dialysis." This proteid, by a careful series of tests, they decided to be a *peptone*, as it answered in a positive manner to all the tests for that body, and gave three reactions in addition not found in any other peptone. It is the only peptone yet known which constitutes a portion of a secretion, or originates within the living body, except as a product of the digestion of proteids.

The second proteid, after a like careful series of experiments, has been determined to belong to the class of *globulins*. The third proteid has not been thoroughly separated, but it is an *albumen*.

These three substances they term *venom peptone*, *venom globulin*, and *venom albumen*.

The venom peptone is not as poisonous as venom, but produces remarkable local effects. If injected, in a small quantity, into the breast muscles of a pigeon, a lump forms, and within forty-eight hours a gangrenous cavity is formed giving off horrible putrefactive odours. The venom globulin is of intense virulence. One-twentieth of a grain will kill a large pigeon in two hours. It is not yet known whether the venom albumen is poisonous. The power of the venom peptone to produce putrefaction in the tissues is most surprising. The venom globulin produces rapid extravasation of blood in the tissues.

The crotalus, whose venom was thus analyzed, was the C. adimanteus, or diamond-back rattlesnake. In his former experiments, Dr. Mitchell employed the C. durissus, and he has made a singular discovery, namely, that while the venom of C. durissus was scarcely at all impaired by boiling, yet the toxicity of C. adimanteus was destroyed by a temperature of 176° F. The report states, also, that the poisons of the rattlesnake, the copperhead, and the moccasin can be destroyed by bromine, iodine, bromohydric acid, sodium hydrate, potassium hydrate, and potassium permanganate. This discovery of the separation of venom requires a long and elaborate series of researches to thoroughly elucidate it.

With this abstract of the extremely important discovery of Drs. Mitchell and Reichert terminates this account of recent experiments on serpent venom.

It will be observed that, in some instances, the conclusions of these investigators seem to be antagonistic, and the remedies, which are all powerful in the hands of some, appear to fail in those of others. Still, great progress has been made in determining the mode of action of venom and defining its chemistry, and a reasonable hope seems permissible that a chemical antidote has been discovered which may save many lives.